



## Sanofi-aventis and Regeneron Announce Results from Phase 2 Study with Aflibercept (VEGF Trap) in Advanced Ovarian Cancer Patients with Recurrent Symptomatic Malignant Ascites

June 11, 2009

Sanofi-aventis and Regeneron Announce Results from Phase 2 Study with Aflibercept (VEGF Trap) in Advanced Ovarian Cancer Patients with Recurrent Symptomatic Malignant Ascites PARIS & TARRYTOWN, N.Y.--(BUSINESS WIRE)--Jun. 11, 2009-- Sanofi-aventis (Euronext: **SAN** and NYSE: **SNY**) and Regeneron Pharmaceuticals, Inc. (Nasdaq: **REGN**) today announced that advanced ovarian cancer patients with recurrent symptomatic malignant ascites (SMA) receiving aflibercept (VEGF Trap) in a randomized, placebo-controlled Phase 2 study experienced a statistically significant improvement in the primary study endpoint, mean time to first repeat paracentesis (removal of fluid from the abdominal cavity), versus placebo control. Symptomatic malignant ascites is an abnormal build-up of fluid in the abdominal cavity in patients with advanced cancer.

Mean time to first repeat paracentesis following a baseline procedure was 55 days with aflibercept as compared to 23 days for patients receiving placebo ( $p=0.0019$ ). Time to first repeat paracentesis was defined as the number of days between study randomization and the first post-randomization paracentesis or, in cases where there was no repeat paracentesis, study withdrawal, death, or six months from randomization.

There was a similar incidence of deaths in both treatment groups (no statistically significant difference; hazard ratio 1.02). In this late-stage patient population with advanced ovarian cancer who were heavily pre-treated (median of four prior courses of chemotherapy), four fatal events were assessed by the investigators as aflibercept treatment related, including one case each of intestinal perforation, dyspnea, pneumonia, and cause unknown.

The types and frequencies of adverse events reported with aflibercept in this study were generally consistent with those reported in clinical studies with other anti-VEGF therapies in advanced ovarian cancer patients.

"The results of this Phase 2, placebo-controlled study demonstrate that aflibercept is a clinically active agent in patients with advanced ovarian cancer with symptomatic malignant ascites. However, given the small number of patients enrolled in this study and the fragile health status of these advanced ovarian cancer patients, who had a median survival of only about three to four months, it is difficult to definitively assess the overall clinical benefit that might be derived from treatment in the real-world clinical practice setting," stated George D. Yancopoulos, M.D., Ph.D., President of Regeneron Research Laboratories. "Therefore, we and sanofi-aventis have decided not to submit these Phase 2 data for accelerated approval in symptomatic malignant ascites. We will focus our efforts on completing the current Phase 3 program which combines aflibercept with standard chemotherapy regimens for the treatment of earlier stage metastatic colorectal, non-small cell lung, pancreatic, and prostate cancers, which should begin delivering data in 2010."

### About the Phase 2 Study

This double-blind, placebo-controlled, multi-center Phase 2 trial enrolled 55 patients with symptomatic malignant ascites, related to advanced ovarian cancer, who had failed a prior platinum-based chemotherapy regimen and who had also received chemotherapy treatment with either liposomal doxorubicin or topotecan. All patients had to have undergone between one and four prior paracenteses in the month prior to randomization in addition to a baseline procedure. Twenty-nine patients were randomized to receive aflibercept administered intravenously as 4 milligrams per kilogram of patient body weight (mg/kg) and 26 patients were randomized to placebo. Patients were dosed every two weeks. In this study the double-blind treatment period was defined as the earliest of the date of death, withdrawal from the study, six months, or entry into open-label treatment. All patients were offered the opportunity to receive open-label aflibercept after 60 days of double-blind treatment provided that at least one post-randomization paracentesis had occurred.

There was a statistically significant 2.4-fold lengthening of time to first repeat paracentesis with aflibercept as compared to placebo. Pre-specified secondary endpoint results were consistent with this primary endpoint finding. The frequency of paracentesis over the first 60 days of the study was reduced, on average, by nearly 50 percent in patients receiving aflibercept versus those receiving placebo ( $p=0.0035$ ). Patient-reported symptoms of ascites, including abdominal discomfort, pain, and bloating, as well as patients' ability to move, were recorded daily from the time of randomization to the time of first repeat paracentesis. Among those patients for whom baseline and follow-up data were available, the cumulative symptoms score results demonstrated a statistically significant improvement in symptoms with aflibercept as compared to placebo.

Severe (Grade 3 or 4) adverse events (AEs) that occurred at a frequency of at least 10 percent in patients who received either aflibercept or placebo were as follows (aflibercept vs. placebo): fatigue or asthenia (13% vs. 44%), dyspnea (20% vs. 8%), peripheral edema (7% vs. 12%), anorexia (7% vs. 12%), dehydration (10% vs. 12%), and hypocalcemia (10% vs. 0%). Grade 3/4 hypertension and proteinuria occurred at a frequency of 7 percent in the aflibercept group. There were four fatal gastrointestinal events reported in the double-blind period of the study. The events include three intestinal perforations in the aflibercept group (10 percent of aflibercept safety population; only one of which was assessed by the investigators as treatment related) and one intestinal fistula in the placebo group (4 percent of placebo safety population).

The results reported are from a preliminary analysis. A full analysis of the final study results will be presented at a future medical meeting.

### **About Symptomatic Malignant Ascites**

Symptomatic malignant ascites is an abnormal build-up of fluid in the abdominal cavity in patients with advanced cancer. In ovarian cancer patients, malignancies can spread throughout the abdominal cavity. In these patients the accumulation of fluid is the result of increased vascular permeability and blockage of the lymphatic channels that regulate the volume of intraperitoneal fluid. Ascites can cause pain, discomfort, limitations on mobility, interference with normal breathing, and other symptoms that impact patients' ability to function. Paracentesis, a common surgical procedure used to remove excess fluid from the abdominal cavity in patients with advanced ovarian cancer, can provide immediate symptomatic relief, but its effects are generally short-lived; on average, several liters of fluid need to be withdrawn as often as every one to two weeks. Paracentesis can be associated with hypotension, peritonitis, pulmonary embolism, visceral/vascular injury, and malnourishment.

### **About Aflibercept (VEGF Trap)**

Aflibercept is an antiangiogenesis inhibitor with a unique mechanism of action. This fusion protein binds all forms of Vascular Endothelial Growth Factor-A (VEGF-A), VEGF-B, and placental growth factor (PlGF), another angiogenic growth factor that appears to play a role in tumor angiogenesis and inflammation. Aflibercept has been shown to bind VEGF-A, VEGF-B, and PlGF with higher affinity than their natural receptors.

### **About the Phase 3 Development Program for Aflibercept**

Aflibercept is currently in Phase 3 clinical development in combination with standard chemotherapy in the following indications:

- VELOUR study: 2<sup>nd</sup>-line metastatic colorectal cancer in combination with fluorouracil, leucovorin, and irinotecan (FOLFIRI)
- VITAL study: 2<sup>nd</sup>-line non-small cell lung cancer in combination with docetaxel
- VANILLA study: 1<sup>st</sup>-line pancreatic cancer in combination with gemcitabine
- VENICE study: 1<sup>st</sup>-line hormone-refractory metastatic prostate cancer in combination with docetaxel and prednisone

Each study is over 60 percent enrolled. Initial data from the Phase 3 program is expected to begin to be available in 2010.

### **About sanofi-aventis**

Sanofi-aventis, a leading global pharmaceutical company, discovers, develops, and distributes therapeutic solutions to improve the lives of everyone. Sanofi-aventis is listed in Paris (EURONEXT PARIS: SAN) and in New York (NYSE: SNY).

### **About Regeneron Pharmaceuticals, Inc.**

Regeneron is a fully integrated biopharmaceutical company that discovers, develops, and commercializes medicines for the treatment of serious medical conditions. In addition to ARCALYST® (rilonacept) Injection for Subcutaneous Use, its first commercialized product, Regeneron has therapeutic candidates in clinical trials for the potential treatment of cancer, eye diseases, inflammatory diseases, and pain, and has preclinical programs in other diseases and disorders. Additional information about Regeneron and recent news releases are available on Regeneron's web site at [www.regeneron.com](http://www.regeneron.com).

### **Forward Looking Statement - sanofi-aventis**

*This press release contains forward-looking statements as defined in the Private Securities Litigation Reform Act of 1995, as amended. Forward-looking statements are statements that are not historical facts. These statements include product development, product potential projections and estimates and their underlying assumptions, statements regarding plans, objectives, intentions and expectations with respect to future events, operations, products and services, and statements regarding future performance. Forward-looking statements are generally identified by the words "expects," "anticipates," "believes," "intends," "estimates," "plans" and similar expressions. Although sanofi-aventis' management believes that the expectations reflected in such forward-looking statements are reasonable, investors are cautioned that forward-looking information and statements are subject to various risks and uncertainties, many of which are difficult to predict and generally beyond the control of sanofi-aventis, that could cause actual results and developments to differ materially from those expressed in, or implied or projected by, the forward-looking information and statements. These risks and uncertainties include among other things, the uncertainties inherent in research and development, future clinical data and analysis, including post marketing, decisions by regulatory authorities, such as the FDA or the EMEA, regarding whether and when to approve any drug, device or biological application that may be filed for any such product candidates as well as their decisions regarding labeling and other matters*

*that could affect the availability or commercial potential of such products candidates, the absence of guarantee that the products candidates if approved will be commercially successful, the future approval and commercial success of therapeutic alternatives as well as those discussed or identified in the public filings with the SEC and the AMF made by sanofi-aventis, including those listed under "Risk Factors" and "Cautionary Statement Regarding Forward-Looking Statements" in sanofi-aventis' annual report on Form 20-F for the year ended December 31, 2008. Other than as required by applicable law, sanofi-aventis does not undertake any obligation to update or revise any forward-looking information or statements.*

#### **Forward Looking Statement - Regeneron Pharmaceuticals, Inc.**

*This news release discusses historical information and includes forward-looking statements about Regeneron and its products, development programs, finances, and business, all of which involve a number of risks and uncertainties, such as risks associated with preclinical and clinical development of aflibercept, determinations by regulatory and administrative governmental authorities which may delay or restrict Regeneron's ability to continue to develop or commercialize aflibercept, competing drugs that are superior to aflibercept, uncertainty of market acceptance of aflibercept, the potential for any collaboration agreement, including Regeneron's agreements with the sanofi-aventis Group and Bayer HealthCare, to be canceled or to terminate without any product success, risks associated with third party intellectual property, and other material risks. A more complete description of these and other material risks can be found in Regeneron's filings with the United States Securities and Exchange Commission (SEC), including its Form 10-K for the year ended December 31, 2008 and Form 10-Q for the quarter ending March 31, 2009. Regeneron does not undertake any obligation to update publicly any forward-looking statement, whether as a result of new information, future events, or otherwise unless required by law.*

Source: Regeneron Pharmaceuticals, Inc.

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